Microvascular Embolization Following Polidocanol Microfoam Sclerosant Administration

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BACKGROUND. Intravenous microfoam sclerotherapy solutions can potentially cause cerebrovascular arterial embolization.

OBJECTIVE. To determine the relationship between polidocanol microfoam formulation and arteriolar embolization bubble lodging and clearance in vivo.

METHODS. Three polidocanol microfoams (one made by the double-syringe method using air and two Varisolve (Provensis, Inc., West Conshohocken, PA, USA) formulations using different physiologic gas mixtures composed primarily of oxygen and carbon dioxide and dispensed from a proprietary canister mechanism) were mixed with venous blood and injected into the rat cremaster arterial microcirculation. Bubble dimensions and dynamics were recorded using intravital microscopy.

RESULTS. Bubble entry frequency, size, and dynamics depended on microfoam formulation. Air-based bubbles (2.72 ± 1.38 nL; n = 21) lodged, obliterating blood flow. Varisolve bubbles (0.20 ± 0.02 nL; n = 2 and 0.53 ± 0.27 nL; n = 27 for the two gas compositions) entered but either did not lodge or cleared within seconds. Bubble size and number were different among these microfoams.

CONCLUSIONS. Both Varisolve formulations produced smaller embolism bubbles than occurred with air-based microfoam. Rapid clearance of Varisolve bubbles suggests that they are so small that they do not have adequate surface area available for significant binding interactions with arteriolar endothelium. Larger air-based bubbles obstruct arteriolar vessels and block blood flow.

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SCLEROTHERAPY IS a common clinical treatment to eliminate intracutaneous, subcutaneous, and transfascial varicose veins and to eradicate venous malformations. Injection of liquid sclerosant has been shown to obliterate varicose veins and improve venous hemodynamics.[1] Sclerotherapy provokes endothelial injury, which transforms the venous structure into a fibrous cord that cannot be recanalized.[2] There has been a recent upsurge in the use of foamed sclerosant preparations.[3–6] Compared with liquid sclerosants, foams have a large coverage surface area, thus increasing endothelial exposure. Foam sclerotherapy leads to a more satisfactory clinical outcome than does liquid sclerotherapy,[7–9] although no specific standards apply to the treatment of venous diseases.[10]

Although apparently safe and effective in providing great success at low cost and with few major complications,[11] foam injection does have risks. One potential risk is cerebrovascular gas embolization resulting from foam traversing a patent foramen ovale (PFO).[12] The German Society of Phlebology's guidelines for varicose vein sclerotherapy state that "in the case of known symptomatic open oval foramen, special caution should be used."[13] Some elements of these precautionary words must be focused on the many details involved in the production and administration of safe and effective sclerosants and their relationship to cerebrovascular arterial gas embolization. Examples include which gas mixtures used in foam production preferentially influence the rate of embolism bubble absorption and which methods of foam agitation create appropriately sized bubbles to minimize the risks of cerebrovascular blood flow obstruction.

We hypothesized that arterial embolization pattern (microbubble volume, diameter of vessel embolized, num-

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ber of bubbles trapped) and dynamics (bubble dissolution, displacement further into the periphery) depended on microfoam gas composition, foam volume injected, and foam agitation method. We anticipated that foam gas composition and careful control of bubble size would produce bubble conformations favoring more rapid bubble clearance and speeding restoration of blood flow. We tested these hypotheses by injecting three different polidocanol microfoams into the rat cremaster arterial microcirculation. We used intravital microscopy to measure bubble dimensions and number following embolization, bubble conformational changes postembolization, and the effects of the sclerosant agent on arterial blood vessel reactivity.

Methods

Animal Model Preparation

Adult male Wistar rats (n = 22; 202–340 g) were handled according to specifications set forth by The University of Pennsylvania Animal Care and Use Committee, in conformance with National Institutes of Health guidelines. After induction of anesthesia with halothane in a closed chamber, the rats were placed in a supine position on a specialized Plexiglas tray and were instrumented (tracheotomy; catheter placement into the right jugular vein, right femoral artery, and left carotid artery; right cremaster muscle dissection) for intravital microscopy viewing of the cremaster muscle microcirculation, as we have previously described and illusttated in detail.[14–16] Animals were ventilated (Ventilator Model 683, Harvard Apparatus, Holliston, MA, USA), with 1.2% halothane in an air-O_2 mixture (fraction of inspired oxygen = 0.3). Blood pressure and heart rate were monitored with the carotid PE 50 catheter (Instech Solomon, Plymouth Meeting, PA, USA). The jugular venous catheter (MRE 040, Braintree Scientific, Braintree, MA, USA) was used for fluid administration and aspiration of venous blood for mixing with microfoam. The femoral artery catheter (MRE 025, Braintree Scientific) was positioned so that the cremaster microcirculatory bed blanched on saline injection. This catheter tip position provides a reliable means of directing injectate (eg, saline or venous blood mixed with microfoam) into the cremaster arteriolar microvasculature.[14–16] Temperature was monitored with a rectal thermometer and maintained at 37°C with a heating pad.

Small (10–200 μm in diameter) cremaster vessels were viewed using a videomicroscopy workstation consisting of a compound microscope (Orthoplan II, Leitz, Wetzlar, Germany), video camera (Model CA2063, Microimage Video Systems, Boyertown, PA, USA), video image analyzer and micrometer (Model VIA-150, Boecheler Instruments, Tucson, AZ, USA), monitor (Model PVM-1343MD, Sony, Tokyo, Japan), and video cassette recorder (Panasonic AG1970, Matsushita Electric Industrial, Osaka, Japan). The cremaster was superfused at 2 mL/min with a warmed (34°C), gassed (95% N_2/5% CO_2) Krebs buffer containing 132 mmol/L NaCl, 25 mmol/L $NaHCO_3$, 5 mmol/L KCl, 1.2 mmol/L $MgCl_2$, and 2 mmol/L $CaCl_2$. The cremaster muscle was given 30 minutes to equilibrate before any experimentation was begun. To demonsttate preservation of robust vascular responses following cremaster muscle preparation, separate 0.5 mL boluses of 10^{-4} mol/L acetylcholine (Sigma Chemicals, St. Louis, MO, USA) and phenylephrine (Sigma Chemicals) were diluted in a Krebs buffer and added topically to the tissue. At least 10 minutes passed after the use of each agent before another agent was applied or before foamed sclerosant was injected. This time lag allowed for complete elimination of the topical agent and total restoration of native vessel tone without influencing bubble passage.[14–16] Tissue responses were considered intact if phenylephrine elicited at least a 20% decrease in vessel diameter and if acetylcholine elicited at least a 50% increase in diameter from baseline. Animals not meeting these criteria were not studied further.

Vessel Reactivity Following Liquid Polidocanol Administration

Four animals were prepared as described above. Aqueous 3% liquid polidocanol (30 mg/mL; Kreussler Pharma GmbH, Wiesbaden, Germany) was injected intravenously (1 μL/g body weight). Vascular responses to topical acetylcholine and phenylephrine were measured at baseline and from 5 to 75 minutes after polidocanol dosing.

Polidocanol Microfoam Preparation

Microfoam was prepared from 1% polidocanol in three different ways. A double-syringe system was employed to create air-based foam with a polidocanol to air ratio of 1:4. A 0.22 μm filter and two 3 mL syringes were attached to a three-way stopcock. One syringe contained 500 μL of liquid polidocanol (10 mg/mL; McGuff Compounding Pharmacy Services, Inc., Santa Ana, CA, USA). Room air (2 mL) was aspirated through the filter into the other syringe. The stopcock valve was turned, and the liquid was agitated into foam between the syringes, as described by Hamel-Desnos and colleagues.[8] The other two microfoam preparations studied use the "two-canister" Varisolve system developed by Provensis, Inc. (West Conshohocken, PA, USA). The difference in their manufacturing process involving pressurization of the canister led to the production of two different proprietary gas mixtures for foam formation, which are referred to as Varisolve type A and Varisolve type B. The exact formulation is a matter of protected intellectual property, but the two are slightly different mixtures of physiologic gases, both containing principally oxygen and carbon

dioxide, as opposed to room air, which is, within reason, 79% nitrogen and 21% oxygen. In all cases, foam was produced and dispensed immediately before its introduction into the syringe and tubing connector assembly for embolization.

Cremaster Arterial Embolization with Polidocanol Microfoam-Laden Venous Blood

A semiclosed syringe and tubing assembly including the femoral arterial and jugular venous catheters was used for mixing, monitoring, and delivering the injectate, as shown in Figure 1. Tubing sections (MRE 040, Braintree Scientific) were joined with stainless steel three-way connectors (Small Parts, Inc., Miami Lakes, FL, USA) and were kept short to minimize dead space. Clamps in each section allowed selection of distinct paths for venous blood aspiration, addition of microfoam, and injection of foam-laden venous blood into the cremaster arterial circulation. Tubing was flushed with 0.9% NaCl solution containing 10 U/mL heparin sulfate to keep it free from blood clots and clear of bubbles, except those emanating from the microfoam.

The hub of a tuberculin syringe was sealed to contain two tubing section ends. One section could be directed toward the femoral arterial line or the jugular venous catheter (or flush syringe). The other section was connected to a flush syringe or a 500 µL gas-tight microsyringe (Model 1750, Hamilton Company, Reno, NV, USA) used to introduce microfoam into the circuit. The tuberculin syringe was loaded with five di-para-xylylene–coated stainless steel magnetic tumble stirring disks (Model VP 722F, V&P Scientific, Inc., San Diego, CA, USA). This syringe rested above a magnetic tumble stirrer (Model VP 710C1CE, V&P Scientific).

An 8 MHz Doppler device (Super Dopplex II, Huntleigh Healthcare Limited, Luton, Bedfordshire, United Kingdom) equipped with an 8 MHz high-sensitivity probe (Model VP8HS, Huntleigh Healthcare Limited) was used to monitor the femoral artery catheter for passage of bubbles during injections. The probe tip was inserted into a thin-walled tube filled with ultrasound gel. The femoral line passed transmurally through the gel-filled tube, making a 30-degree angle with the Doppler probe tip. Audio output from the Doppler device was input into the videorecorder, providing synchronized ultrasound audio and videomicroscopy image recordings during injections.

Animals ($n = 6$ per group) were randomly assigned to receive one microfoam product. Venous blood was withdrawn into the tuberculin syringe. The gas-tight microsyringe was loaded with microfoam, which was then added into the tuberculin syringe and stirred for 30 seconds. The microfoam-blood mixture was then injected through the femoral artery catheter. Microfoam dosing began at 50 µL in 200 µL of blood and was then increased by 100 µL of foam from 100 to 400 µL in 400 µL of blood. Small (~ 100 µL) boluses of injectate were delivered every 5 to 7 seconds until the syringe was empty. The injection ceased if bubbles were observed in the video viewing field. Otherwise, saline boluses were injected after each completed dose to demonstrate blanching and reconfirm the adequacy of the catheter tip position. In some cases in which the dosing schedule was completed without embolization being observed, microfoam alone was then injected.

If cremaster embolization was observed, entrapped bubbles were sought in the embolized artery and videotaped over time. If entrapped bubbles became dislodged, movements into the periphery were continuously tracked and recorded. Bubbles were observed until visualization was no longer possible either owing to complete absorption or movement to a less favorable viewing area. Bubble and vessel dimensions were measured from the videotape using the videomicrometer. Bubble volume was calculated assuming axisymmetry and a representative geometry consisting of a cylindrical core crowned with a hemispherical cap on each end.[14-18]

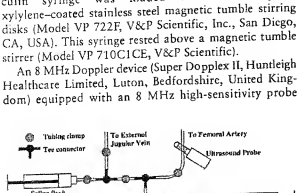

Figure 1. Schematic of mixing syringe and tubing connector assembly.

Statistical Analysis

The results are presented as arithmetical mean ± standard deviation. Group variances were examined using the F test. For equal variances, statistical significance was established using analysis of variance, with $p < .05$ considered statistically significant using the Bonferroni correction. For vessel reactivity tests, changes within the same group at different time points were considered statistically significant for $p < .05$ using the paired Student's t-test. The variances were not equal for analysis of the embolism bubble volumes with different microfoam formulations. In this case, the t-test for unequal variances was used to compare specific group means.

Results

Vessel Reactivity Following Liquid Polidocanol Administration

Vasodilation and vasoconstriction responses following liquid polidocanol administration are shown in Figure 2. Dilation after acetylcholine application exceeded 50% in each case, with no differences found in response at the 5-, 30-, or 60-minute time points compared with the baseline measurement (see Figure 2A). No differences were detected in vessel constriction following phenylephrine delivery at the 20-, 45-, and 75-minute time points compared with the baseline value, with vessel constriction exceeding 20% in each case (see Figure 2B).

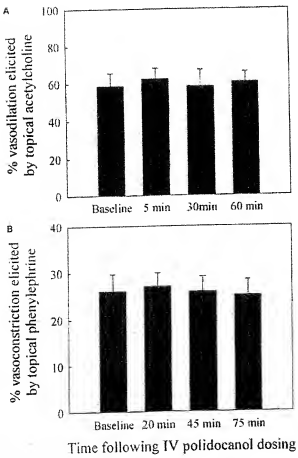

Figure 2. (A) Vasodilator response to topical application of acetylcholine. (B) Vasoconstrictor response to topical application of phenylephrine. $n = 4$ per group.

Cremaster Arterial Embolization with Polidocanol Microfoam-Laden Venous Blood

Audio signals indicating bubble passage past the ultrasound probe were detected with every injection of venous blood mixed with microfoam. There was no visual evidence of gas embolization of vessels in the viewing field on every injection. Visible embolization events were both dose and agent dependent, as seen in Figure 3. Visible bubble embolization occurred in all six air-based microfoam experiments. Four of the six embolization events occurred at low doses of either 50 µL of microfoam in 200 µL of blood or 100 µL of microfoam in 400 µL of blood. For Varisolve type A, embolization was seen in five of the six experiments, all at doses of 300 or 400 µL of microfoam in 400 µL of blood. In one case for Varisolve type A, the entire dosing schedule was exhausted without bubble entry being seen. With Varisolve type B microfoam, visual confirmation of bubble embolization was made in one of six experiments at a microfoam dose of 300 µL in 400 µL of blood. Only two bubbles were seen entering the arterial circulation. The dosing schedule was otherwise completed without visual evidence of bubble entry.

The size distribution of bubbles entering the cremaster circulation also depended on the microfoam agent injected. Tables 1 and 2 show the mean values and ranges of bubble volumes and dimensions observed for each study agent. The largest bubbles occurred with the air-based microfoam and had volumes 5 to 30 times greater than those seen with the Varisolve microfoams. The dimensions of 21 separate air-based microfoam bubbles, which all lodged proximally in the primary arterial vessel feeding the

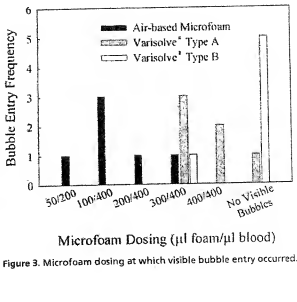

Figure 3. Microfoam dosing at which visible bubble entry occurred.

cremaster, were determined. Although bubbles were also found in vessels down to the capillaries, bubble dimensions were determined only from bubbles occupying, and not transiting, the largest and most proximal vessels.

With injection of microfoam from the two Varisolve formulations, visible bubbles transited the arteriolar vasculature without lodging. Data for bubble size distribution and number were obtained from video images of bubbles entering and transiting the microscope field of view. Twenty-seven bubbles were observed with Varisolve type A injections, and only two bubbles were seen in the Varisolve type B experiments. Since bubbles in these groups did not lodge, statistical comparisons to the air-based microfoam results have not been made.

Table 1. Embolism Bubble Volumes

Microfoam Formulation	*Bubble Volume Mean ± SD (nL)*	*Bubble Volume Range (nL)*	*Number of Bubbles*
Air–based*	2.72 ± 1.38[†‡]	0.93–6.45	21
Varisolve type A[§]	0.53 ± 0.27[‡]	0.2–1.34	27
Varisolve type B[§]	0.20 ± 0.02	0.19–0.22	2

*Data are for bubbles lodged in the main cremaster feeder artery.
†$p < .05$ compared with Varisolve type A.
‡$p < .05$ compared with Varisolve type B.
§Data are for bubbles transiting the cremaster microcirculation.
Lodged bubbles not found for Varisolve types A and B.

Figure 4 shows representative images of intra-arterial microfoam bubbles. The ~ 60 μm diameter arteriole in Figure 4A is completely filled with air-based microfoam bubbles. Individual bubbles tracked over several minutes show very little change in bubble dimensions or positions of bubble interfaces. These bubbles remain entrapped, obstructing blood flow while they reabsorb slowly, without much distal displacement (also known as the stick-and-slip movement[14,15]). Air-based foam bubbles remain evident in these experiments for more than 25 minutes after embolization has occurred. A markedly different behavior occurred with Varisolve type A (see Figure 4B) and type B (see Figures 4C and 5) embolization: bubbles rapidly transited the vasculature. The bubbles shown in Figure 4, B and C, are no longer visible in the next video frame taken one-thirtieth of a second later (not shown). No Varisolve type A or type B bubbles were found in the distal vasculature when moving the microscope stage to scan the cremaster muscle immediately after embolization occurred. With direct femoral artery injection of undiluted Varisolve type B microfoam, a considerable fraction of the cremaster arteriolar bed was filled with bubbles. These bubbles continuously moved distally and visibly lost volume as the gas phase was reabsorbed. Figure 5 shows two images taken 32 seconds apart at slightly different, but overlapping, spatial positions. The large bubble appearing in Figure 5A filled the parent and daughter branches of an arteriolar bifurcation. In Figure 5B, this bubble has cleared completely owing to reabsorption and distal displacement. The vessels have been reperfused with blood. Total clear-

Table 2. Embolism Bubble Dimensions

Microfoam Formulation	*Bubble Diameter (μm)*		*Bubble Length (μm)*	
	Mean ± SD	*Range*	*Mean ± SD*	*Range*
Air based*	127.7 ± 7.5	117–138	125.8 ± 98.8	2–339
Varisolve type A†	79.9 ± 9.5	66–102	46.8 ± 29.5	0–112
Varisolve type B†	70.5 ± 0.7	70–71	4.5 ± 6.4	0–9

*Data are for lodged bubbles found only in the main arterial feeder.
†Data are for bubbles transiting the cremaster microcirculation.
Lodged bubbles not found for Varisolve types A and B.

Figure 4. Microfoam bubbles in the cremeter arterial microcirculation. Arterial blood flow direction is from left to right in all images. (A) Multiple lodged air-based microfoam bubbles obstructing blood flow. (B) Varisolve type A microfoam bubbles transiting the arterioles. (C) A Varisolve type B microfoam bubble transiting the arterioles.

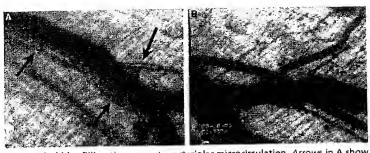

Figure 5. Varisolve type B microfoam bubbles filling the cremaster arteriolar microcirculation. *Arrows* in A show the large gas volume filling the bifurcation. In B, a slightly more distal view appears 32 seconds later with complete clearance of the bubble and vessel reperfusion. The *asterisks* indicate the overlapping regions between the two images.

ance of all bubbles from the arterioles occurred in less than 3 minutes, with complete restoration of blood flow.

Discussion

Intra-arterial gas embolism is a potential complication of foam sclerotherapy for varicose veins owing to bubble passage through a PFO. PFO has a 10 to 35% population incidence,[19] and the majority of patients are asymptomatic and remain undiagnosed. It is critical to evaluate foamed scletosants and their relationship to arterial gas embolization. For the purpose of comparing clinical dosing in humans with the doses administered in this experiment, we consider the extreme case in which an entire sclerosing foam dose of 20 mL was to migrate from the venous depot site to the right atrium of a 60 kg adult patient with a PFO. If 20% of the blood volume entering the right atrium were to cross the PFO, 4 mL of microfoam would enter the systemic arterial circulation. On a volume to weight ratio basis, this is equivalent to 20 µL of intra-arterial foam in a 300 g rat used in this study. Therefore, our study dose levels from 50 to 400 µL represent 2.5 to 20 times the dose that might enter the arterial circulation. These dose equivalence calculations are further amplified by the small volume of tissue of the cremaster muscle compared with the total volume of important end organs, such as the brain and heart. We also administered liquid polidocanol (3%) at a single dose of 1 mL/kg body weight. Based on the human to rat body weight ratio, this represents 56 times the amount of polidocanol (density of 1.6 mg/mL) in the usual therapeutic dose of foam (20 mL).

Microfoams may be produced by a variety of agitation techniques to consist of bubbles initially smaller than 250 µm. Foams are inherently unstable, and they break down and coalesce into larger bubbles. Gas in the venous vasculature following foam sclerotherapy can occupy a much larger range of bubble sizes than were initially present in the foam. Bubbles may enter the arterial circulation before complete gas absorption into surrounding tissues can occur. Both the gas mixture and the method of agitation employed to create foam can influence the size distribution and rate of reabsorption of any arterial embolism bubbles. These factors, as well as direct sclerosant effects, can damage the arterial vasculature, obstruct blood flow, and cause ischemic tissue injury.

We found that direct intravenous injection of the liquid sclerosing agent did not alter arterial vessel reactivity for an hour or more (see Figure 2). This indicates that polidocanol's direct toxic effects on vascular endothelium result from localized exposure to higher concentrations than those to which the arterial microcirculation was exposed in our experiments. Dilution of the dose delivered into the specimen's circulating blood volume (65 µL/g for rats) produced arterial concentrations of ~ 0.05%, considerably less than the therapeutic concentration described in clinical guidelines for treating venous diseases.[13] Based on the preservation of vascular responses, we conclude that a normal arterial and arteriolar endothelium was present during microfoam embolization. We also conclude that the various interfacial surface interactions and binding mechanisms that we have previously described as contributing to capturing bubbles within the microcirculation were preserved.[14,15,20,21]

One major contributor to bubble lodging is the surface area available for surface interactions with the endothelium. Larger bubbles present a greater surface area to the endothelium and therefore exert more shearing force that slows bubble motion. Slower bubble motion and a large surface area allow sufficient contact time for critical adhesion forces to be established between the endothelial and bubble surfaces,[20,21] arresting bubble motion altogether. The results in Tables 1 and 2 demonstrate that air-based microfoam yielded the largest bubbles.

The gas mixture used to create the bubbles is also a factor in the embolism frequency observed (see Figure 3) and bubble dimensions cataloged (see Tables 1 and 2). Based on our previously published theoretical models,[14–18] it is expected that a 2.72 nL (~ 173 µm diameter) air bubble (the average air-based bubble size) will persist for at least 9.2 minutes. This is much longer than the

time needed in the experiments (less than a minute) to add microfoam to the venous blood sample, stir for 30 seconds, and inject through the femoral catheter. The long bubble lifetime permits injection into and trapping within the cremaster microcirculation. Bubble lifetime is shorter if the oxygen concentration within the bubble is increased and the nitrogen concentration is decreased. It is not surprising, then, that much smaller bubbles entered the cremaster circulation when Varisolve microfoam was reintroduced. A 0.53 nL (~ 100 μm diameter) bubble, representative of the average Varisolve type A bubble found, would persist for approximately 3.1 minutes if it were composed of room air (ie, 79% nitrogen), but it would reabsorb in under 1 minute if composed of the Varisolve type A proprietary physiologic gas formulation composed primarily of oxygen and carbon dioxide. Similarly, a 0.20 nL (~ 73 μm diameter) bubble, representative of the Varisolve type B bubbles found, would persist for approximately 1.6 minutes if composed of room air, but it would reabsorb in under 30 seconds if composed of the proprietary gas mixture (primarily oxygen and carbon dioxide) used to formulate Varisolve type B. This suggests why many bubbles could be audibly detected using the ultrasound probe but could not concomitantly be seen entering the cremaster microcirculation. Bubble shrinkage to sizes far smaller than the monitored arteriolar diameter can occur during the stirring phase prior to intra-arterial injection. Some of these microbubbles are evident on individual frame-grabbed videomicroscopy images but cannot be appreciated during conduct of the actual experiment or in the moving video. At lower microfoam doses, the total gas load of the bubbles is better solubilized and bubbles may become well separated spatially, reducing coalescence. At higher microfoam doses, the greater total gas load is less well accommodated in the venous blood sample during mixing. Bubbles slowly decrease in size owing to the smaller concentration gradients promoting gas absorption. The larger number of bubbles present also decreases their separation distance, making it more likely that coalescence, coupled with decreased absorption, will result in some larger bubbles being present.

Because of the lower nitrogen content in their formulation, more rapid absorption of Varisolve bubbles occurs. This, in part, accounts for why no smaller emboli could be found in the periphery after bubbles transited the monitored vessels. Another factor contributing to their absence in the periphery is that the bubble interface is coated with polidocanol, which acts as a surface tension-reducing agent, or surfactant. We have previously shown in vivo,[14,15] in excised vessels,[21] and in vitro[22,23] that surfactants reduce adhesion between a bubble surface and the vessel wall. Surfactants promote more rapid bubble clearance, accelerate bubble absorption, and result in earlier vessel reperfusion in gas embolism. Surfactants present on the bubble surface reduce, but do not eliminate, adhesion interactions between the bubble and endothelial surfaces. Although the same surfactant was present with all three microfoam formulations, the significantly larger air-based microfoam bubbles presented a sufficiently large surface area for adhesion and bubble lodging to have occurred. Yet even the smaller Varisolve bubbles must deform into more narrow and elongated shapes with increasing surface area as they pass into smaller and smaller distal arterioles. That no Varisolve bubbles were detected to have lodged in small peripheral vessels indicates that the surfactant effect of decreasing adhesion force played a substantial role in Varisolve bubble behavior.

We have demonstrated that microfoams not formulated with air and double-syringe agitation introduced fewer and smaller embolism bubbles, which did not obstruct arterial microcirculatory blood flow. As the clinical role of foam sclerotherapy to treat venous diseases is pursued, attention must be given to foam physical factors, such as gas composition and bubble size. This will help improve the safety profile regarding the risks of arterial embolization and refine guidelines for use in the general population in which an undiagnosed PFO is prevalent.

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